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# Serum Vitamin A and Subsequent Development of Prostate Cancer in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study[1]

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## ABSTRACT

**The relation between serum vitamin A measurements made at baseline examination (1971–1975) and subsequent development of prostate cancer was examined in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (1981–1984). The analytic cohort consisted of 2440 men 50 years of age or older who were followed for a median of 10 years. A total of 84 men developed prostate cancer. The mean level of serum vitamin A was significantly lower ($P < 0.01$) in prostate cancer cases than in noncases. Considered as a continuous variable or in quartiles, a statistically significant ($P < 0.005$ or $P < 0.02$, respectively) trend was observed for increased risk of prostate cancer with decreasing levels of serum vitamin A. Adjusted for age and race, men in the lowest quartile had a relative risk of 2.2 (95% confidence intervals, 1.1, 4.3) compared to those in the highest quartile. The elevated risk of prostate cancer associated with the lowest quartile of serum vitamin A levels did not attenuate with increasing time between blood drawing and diagnosis, suggesting that metabolic effects of early disease are an unlikely explanation of these results. The inverse association between serum vitamin A and prostate cancer incidence was independent of age at examination and several other possible confounding variables. This is the first prospective study of serum vitamin A and prostate cancer to include a large (84) number of cases.**

## INTRODUCTION

Among American men, cancer of the prostate is the most prevalent form of cancer and the second leading cause of cancer death (1). Its incidence increases more rapidly with advancing age than any other cancer, rarely being diagnosed before age 50 years (2, 3).

Little is known about the etiology of prostate cancer. Hormonal factors involving androgen metabolism are suspected, but epidemiological studies have not given consistent results. Dietary variables, including fat and micronutrients, have been implicated in some studies but the results are not conclusive (4, 5).

To date, four studies of serum vitamin A and prostate cancer have been carried out (6–9). In a recent case-control study of 130 prostate cancer cases, Hayes *et al.* (6) reported that serum vitamin A levels were significantly lower in cases than in controls. In addition, a significant trend of increased prostate cancer risk with decreasing serum vitamin A levels was found. Because of the case-control design, Hayes *et al.* (6) could not exclude the possibility that their finding was due to the effect of disease and/or associated treatment on serum vitamin A levels. Three other studies of prostate cancer, two case-control and one prospective, did not find a significant association with serum vitamin A levels, but the results were based on small numbers of prostate cancer cases (7–9).

We have investigated the relation between serum vitamin A levels and prostate cancer using the NHANES[3] I Epidemiologic Follow-up Survey (NHEFS) (10), a prospective study in which serum vitamin A measurements were available for a large number (84) of men who subsequently developed prostate cancer.

## SUBJECTS AND METHODS

NHANES I was carried out from 1971 to 1975 by the National Center for Health Statistics to provide cross-sectional data pertaining to health status and nutrition on a probability sample of the civilian, noninstitutionalized population of the United States (11). Groups at high risk of malnutrition, including children, women of child-bearing age, the elderly, and low income individuals, were oversampled. The NHEFS was designed to provide data on subsequent health outcomes and habits of individuals ages 25 years or older at the time of NHANES I. Tracing and reinterview of these individuals occurred between 1981 and 1984. Of the 14,407 individuals eligible for participation in NHEFS, 94% of the 5,811 men and 92% of the 8,596 women were successfully traced.

This analysis was limited to the 3226 males who were 50 years old or older at baseline examination. Ninety-one of these could not be traced. One hundred nine subjects were found alive but could not be reinterviewed due to refusal or inability to recontact, preventing identification of previous hospitalizations. This represents a 6.2% loss to follow-up. Additional sequential eliminations of men were made: 582 due to missing serum vitamin A data; and 4 who were prevalent cases. Use of the age 50 cutoff eliminated only 1 case of prostate cancer. The analytical cohort thus consisted of 2440 men, of whom 84 developed prostate cancer.

Prostate cancer cases were identified by hospitalization and/or death certificate records coded using the eighth revision of the International Classification of Disease (12). For cases identified through hospital records, the date of first admission for prostate cancer listed in the discharge diagnoses was regarded as the incidence data. The ratio of observed to expected cases for men 50 years of age or older, based on age/sex/race-specific incidence rates from the Connecticut Tumor Registry, was 1.23 (95% confidence interval, 0.99–1.50).

The NHANES I included questionnaires, a physical examination, and collection of blood and urine specimens. Blood was drawn by venipuncture. Sera for vitamin A assessment were separated from clots within 1 h of clotting. Hemolyzed sera were not pooled with sera from other tubes. Sera for vitamin A analysis were stored at −20°C and were not subjected to repeated freezing and thawing. In most cases the

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[3] The abbreviations used are: NHANES, National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Survey; RBP, retinol-binding protein.

storage period did not exceed 3 months. Serum vitamin A analyses were performed by a modification of the method of Neeld and Pearson (13, 14). This involves measuring the transient blue color formed in the reaction between trifluoroacetic acid and vitamin A at 620 nm. A quality control problem, believed to be due to a contaminated batch of chloroform, arose during a 6-month period in 1972. Mean serum vitamin A values for the quality control pool were elevated, although not outside quality control limits. This problem was resolved by an Expert Panel on Vitamin A Nutriture convened by the Federation of American Societies for Experimental Biology in collaboration with the Food and Drug Administration and by the National Center for Health Statistics (15). It was decided to adjust sample values of serum vitamin A determined during the quality control problem period. Analyses of unadjusted and adjusted periods reflected no systematic biases in the pattern of differences for the 25th, 50th, and 75th percentiles within or among any of the age/sex/race groups examined. Also, prevalence estimates for low serum vitamin A levels were similar regardless of whether they were based on adjusted or unadjusted vitamin A data. Quality control procedures and a comparison of trifluoroacetic acid and high pressure liquid chromatography methods used in the NHANES program have been reviewed by the expert panel described above (15).

To circumvent this problem two analytical cohorts were examined in this study. The first, using only unadjusted serum vitamin A values, was composed of 1960 subjects yielding 70 cases. The second, using both unadjusted and adjusted serum vitamin A values, consisted of 2440 individuals of whom 84 developed prostate cancer. Since no major differences were observed between these two cohorts, data from the larger, combined cohort are presented here.

Covariate data (Table 1) were obtained from the baseline interview (1971–1974) except for smoking status, which, when unavailable from baseline data, was inferred from follow-up interview (1981–1984).

Quartiles of serum vitamin A were determined based on the analytical cohort described above. Crude incidence rates were calculated by dividing the number of incident cancers by the total number of person-years in the cohort. The number of person-years contributed by an individual subject were calculated from baseline to the time of cancer incidence, death, or follow-up interview, whichever came first. Age-adjusted rates were calculated by the direct method (16), with the age distribution of the analytical cohort as the standard. Relative risk of cancer was estimated using Cox's proportional hazards model (17). All regression models were adjusted for age and other variables when indicated. Test for trend in relative risk was based on the statistical significance of a trend variable in the proportional hazards model. The analyses were performed with the PROC PHGLM procedures of the SAS statistical package (18).

## RESULTS

The relation between baseline levels of serum vitamin A and covariates possibly linked to cancer risk is shown in Table 1. A higher percentage of Blacks than Whites was found in the lowest quartile of serum vitamin A for all age groups. The number of Blacks in some age groups was quite small, however. In this cohort, ages 50–74 years at baseline examination, there was little relationship between serum vitamin A and age. Education, serum cholesterol, alcohol consumption, and to a lesser extent body mass index were positively associated with serum vitamin A levels. Individuals taking vitamin and/or mineral supplements showed increased serum vitamin A levels, but information distinguishing clearly between different types of supplements is not available. Marital status, height, total calories, and smoking were unassociated with serum vitamin A levels in this cohort.

A statistically significant ($P < 0.01$) difference of 8.9% was observed in the mean values of serum vitamin A between cases [59.36 ± 15.96 (SD) μg/dl] and noncases [65.14 ± 20.11 μg/dl].

Table 1 *Age-adjusted characteristics of cohort in relation to quartiles of serum vitamin A determined at baseline*

| Variable | N | % of cohort in quartiles of serum vitamin A (μg/dl)[a] 1st (17–51) | 2nd (52–63) | 3rd (64–74) | 4th (75–231) |
|---|---|---|---|---|---|
| Age at baseline (yr) | | | | | |
| 50–59 | 664 | 22 | 25 | 24 | 29 |
| 60–64 | 258 | 23 | 32 | 22 | 23 |
| 65–69 | 884 | 25 | 26 | 24 | 25 |
| 70–74 | 634 | 23 | 27 | 25 | 25 |
| Education (yr) | | | | | |
| <12 | 1595 | 26 | 27 | 24 | 23 |
| 12 | 454 | 21 | 23 | 26 | 30 |
| >12 | 364 | 16 | 27 | 21 | 36 |
| Marital status | | | | | |
| Single | 139 | 30 | 21 | 20 | 29 |
| Married | 1989 | 23 | 27 | 24 | 26 |
| Other | 309 | 27 | 24 | 26 | 23 |
| Tertiles of serum cholesterol (mg/100 ml) | | | | | |
| 75–204 | 817 | 32 | 28 | 19 | 21 |
| 205–242 | 806 | 22 | 27 | 27 | 24 |
| 243–793 | 817 | 17 | 25 | 26 | 32 |
| Tertiles of ht (cm) | | | | | |
| 144.9–169.0 | 816 | 25 | 25 | 22 | 28 |
| 169.1–174.7 | 812 | 24 | 27 | 26 | 23 |
| 174.8–197.6 | 812 | 22 | 27 | 24 | 27 |
| Tertiles of body mass index (wt/ht$^2$) | | | | | |
| 12.97–23.75 | 813 | 29 | 27 | 21 | 23 |
| 23.75–26.97 | 814 | 20 | 26 | 26 | 28 |
| 26.98–52.63 | 813 | 21 | 27 | 25 | 27 |
| Tertiles of total calories | | | | | |
| 299–1489 | 813 | 26 | 26 | 23 | 25 |
| 1490–2069 | 814 | 23 | 28 | 24 | 24 |
| 2071–10978 | 813 | 21 | 26 | 25 | 28 |
| Smoking | | | | | |
| Never | 694 | 23 | 24 | 27 | 26 |
| Former | 703 | 21 | 26 | 25 | 28 |
| Current | 735 | 25 | 30 | 22 | 23 |
| Alcohol consumption | | | | | |
| 0 | 1015 | 26 | 26 | 26 | 21 |
| Low (>0–5 g/day) | 721 | 23 | 32 | 21 | 24 |
| High (>5 g/day) | 698 | 18 | 22 | 25 | 35 |
| Race | | | | | |
| White | 2027 | 21 | 27 | 25 | 27 |
| Black | 382 | 33 | 26 | 18 | 23 |
| Race-Age (yr) | | | | | |
| White | | | | | |
| 50–59 | 561 | 20 | 25 | 25 | 30 |
| 60–64 | 220 | 22 | 33 | 22 | 23 |
| 65–69 | 720 | 24 | 26 | 25 | 25 |
| 70–74 | 526 | 19 | 27 | 27 | 27 |
| Black | | | | | |
| 50–59 | 99 | 30 | 26 | 16 | 28 |
| 60–64 | 32 | 34 | 23 | 22 | 21 |
| 65–69 | 149 | 31 | 26 | 18 | 25 |
| 70–74 | 102 | 39 | 28 | 17 | 16 |
| Vitamin/mineral supplements | | | | | |
| No | 1747 | 27 | 28 | 24 | 21 |
| Regularly | 518 | 12 | 23 | 25 | 40 |
| Irregularly | 175 | 20 | 25 | 23 | 32 |

[a] Results in columns are percentages of total person-years for individuals with the variable status which are associated with persons whose serum vitamin A values fall in the given quartile.

Age-adjusted incidence rates for the lowest quartile were significantly higher than for any other quartile, reaching 2.4 times that of the highest quartile (Fig. 1).

Table 2 gives relative risks of prostate cancer by quartile of

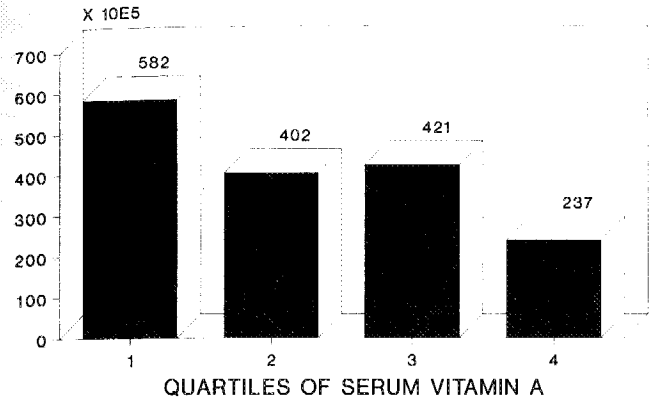


Fig. 1. Age-adjusted incidence rates for prostate cancer by quartiles of serum vitamin A.

Table 2 *Association of baseline serum vitamin A values with subsequent development of prostate cancer*

| Quartiles of serum vitamin A | Cases | RR[a] | 95% CI |
|---|---|---|---|
| 1 (low) | 28 | 2.4 | 1.3, 4.6 |
| 2 | 22 | 1.6 | 0.8, 3.2 |
| 3 | 21 | 1.7 | 0.9, 3.4 |
| 4 (high) | 13 | (1.0)[b] | |
| Analysis for trend | | $\chi^2$ | *P* for trend |
| Serum vitamin A, continuous | | 8.57 | 0.003 |
| Serum vitamin A, quartiles | | 6.20 | 0.012 |

[a] RR, relative risks determined from a proportional hazards model including age at examination and quartiles of serum vitamin A; CI, confidence intervals.
[b] Numbers in parentheses indicate reference groups.

Table 3 *Association of baseline serum vitamin A values with subsequent development of prostate cancer in Blacks and Whites*

| Analytical cohort | Cases | Quartiles of serum vitamin A | Cases | Age-adjusted rate × $10^5$ | RR[a] | CI |
|---|---|---|---|---|---|---|
| Blacks[b] 382 | 24 | 1 (low) | 10 | 995 | 1.4 | 0.5, 4.2 |
| | | 2 | 5 | 649 | 0.9 | 0.3, 3.0 |
| | | 3 | 4 | 713 | 1.0 | 0.3, 3.7 |
| | | 4 (high) | 5 | 747 | (1.0)[d] | |
| Whites[c] 2027 | 59 | 1 (low) | 17 | 458 | 2.7 | 1.2, 6.2 |
| | | 2 | 17 | 368 | 2.1 | 0.9, 4.8 |
| | | 3 | 17 | 389 | 2.2 | 0.8, 5.0 |
| | | 4 (high) | 8 | 169 | (1.0) | |

[a] RR, relative risks determined from a proportional hazards model including age at examination and quartiles of serum vitamin A; CI, confidence interval.
[b] *P* for trend = 0.27.
[c] *P* for trend = 0.02.
[d] Numbers in parentheses indicate reference groups.

serum vitamin A. Whether serum vitamin A levels were considered in quartiles or as a continuous variable, a significant negative trend with risk of prostate cancer was observed.

Adjustment for effects of confounders was done by examining multivariate models including all variables listed in Table 1, as well as models including age at examination, quartiles of serum vitamin A, and each variable in Table 1 individually. Only minimal changes in relative risks resulted. The relative risk estimates (and 95% confidence intervals) for the lower three quartiles of serum vitamin A (as compared with the highest quartile) from a multivariate model including age at examination and race were 2.2 (1.1, 4.3), 1.6 (0.8, 3.1), and 1.7 (0.9, 3.4), respectively.

Blacks had an increased risk of prostate cancer compared to Whites in this cohort, the relative risk being 2.2 (1.3, 3.5). The interaction between race and the serum vitamin A-prostate cancer association was examined in more detail (Table 3). For Blacks, only those risks for the lowest quartile were elevated and the test for trend was not significant; however, the referent quartile contained only 5 cases. For Whites, the risks were somewhat higher than for the combined cohort, and a significant trend was seen. Only the relative risk for quartile 1 was significantly different from unity as observed in the combined cohort. Log likelihood ratio tests did not reveal significant interaction effects for race and serum vitamin A.

Several studies have shown increased dietary intake of vitamin A associated with increased risk of prostate cancer only for cases diagnosed at age 70 years or above (19–21). The relationship of serum vitamin A to prostate cancer was examined in men followed from age 70 years or above. Cases identified by death certificate only were excluded from this analysis because date of diagnosis was unavailable. However, the pattern of risk was similar to that observed when all cases were included in the analytical cohort (Table 4). Quantitatively, the relative risks for each quartile of serum vitamin A were higher than when the full analytical cohort was examined. For follow-up only until age 70 years, the relative risk for the lowest quartile compared to the highest was 0.8 (0.2, 2.4). However, this finding was based on a total of only 21 cases.

Because serum vitamin A levels might be influenced by early disease, we examined risk of prostate cancer within strata of follow-up time from baseline to diagnosis (Table 5). Cases identified by death certificate only were excluded from this analysis. However, similar results were obtained when all cases were included. The highest relative risks were observed in the 3.0–5.9-year period from baseline examination to diagnosis. Although a lower relative risk was seen when diagnosis occurred 6 years or more from baseline, there was no trend indicating decreasing risk with increasing time from serum collection until diagnosis.

## DISCUSSION

This is the first prospective study of serum vitamin A and prostate cancer involving a substantial number (84) of cases. The analysis revealed a significant inverse trend between serum vitamin A levels and subsequent incidence of prostate cancer. After adjusting for race and age, men in the lowest quartile of

Table 4 *Association of baseline serum vitamin A values with subsequent development of prostate cancer in men ages 70 years or over at diagnosis: analytical cohort, 1590; cases, 52*

| Quartiles of serum vitamin A | Cases | Age-adjusted rate × $10^5$ | RR[a] | CI |
|---|---|---|---|---|
| 1 (low) | 19 | 590 | 3.6 | 1.4, 8.9 |
| 2 | 14 | 420 | 2.4 | 0.9, 6.3 |
| 3 | 13 | 352 | 2.0 | 0.8, 5.3 |
| 4 (high) | 6 | 168 | (1.0)[b] | |

[a] RR, relative risks determined from a proportional hazards model including age at examination and quartiles of serum vitamin A; CI, confidence interval.
[b] Numbers in parentheses indicate reference groups.

Table 5 *Association of baseline serum vitamin A values with subsequent development of prostate cancer by number of years from baseline to diagnosis*

| Quartiles of serum vitamin A | No. of yr of follow-up (no. of cases)[a] | | |
|---|---|---|---|
| | 0–2.9 (13) | 3.0–5.9 (17) | >/6 (43) |
| 1 (low) | 2.7 (0.5, 13.4) | 4.3 (0.9, 20.1) | 1.6 (0.6, 3.9) |
| 2 | 1.0 (0.1, 6.7) | 1.4 (0.2, 8.6) | 1.5 (0.6, 3.7) |
| 3 | 1.6 (0.3, 9.7) | 2.1 (0.4, 11.7) | 1.4 (0.6, 3.6) |
| 4 (high) | (1.0)[b] | (1.0) | (1.0) |

[a] Entries are relative risks (95% confidence intervals) determined from a multivariate proportional hazards model including age at examination, race, and quartiles of serum vitamin A.
[b] Numbers in parentheses indicate reference groups.

serum vitamin A had a relative risk 2.2 times higher than those in the highest quartile.

The laboratory methodology for measurement of serum vitamin A has undergone substantial change since samples used in this study were measured. However, the mean values reported here for cases and noncases using a modification of the colorimetric method of Neeld and Pearson (13) are in excellent agreement, by comparison of means, with those reported by Hayes *et al.* (6) using more recent high-pressure liquid chromatography technology.

Associations observed in this cohort between levels of serum vitamin A and other covariates are consistent with previously reported relationships. Although serum vitamin A levels have been shown to increase with age throughout life when broad age categories are considered, within the category examined in this cohort there was little association of serum vitamin A with age. Vitamin and/or mineral supplementation has been shown to affect serum vitamin A levels (22, 23), as we also observed in the present cohort. Introduction of multiple covariates into a proportional hazards model did not substantially influence relative risks for prostatic cancer associated with serum vitamin A levels. There was some suggestion of effect modification of risk with age and race, but further studies are needed to clarify these relationships.

Our findings in a prospective study are consistent with the results in a recent retrospective case-control study of prostate cancer (6). Three earlier studies found no significant association between serum vitamin A and prostate cancer, but they were hampered by small numbers of cases (7–9). When all forms of cancer are considered, an inverse association with serum vitamin A was shown in two early prospective studies (24, 25), but extended follow-up of these study groups did not confirm these results (26, 27). A number of other prospective studies [recently reviewed in Ref. 28], examining the risk of all cancers combined or site-specific cancers (8, 29–31), have failed to show an inverse association with serum vitamin A, with the possible exception of special subgroups [e.g., individuals with low selenium levels (29), men who smoke (30)] or particular sites [*e.g.*, gastrointestinal cancer (31)]. However, Wald *et al.* (27) showed that serum vitamin A values were lower only for subjects who developed cancer within 3 years of blood collection, suggesting a metabolic effect of early cancer. This seems an unlikely explanation of our findings, since there was no trend suggesting a decreasing risk of low serum vitamin A levels with increasing time until diagnosis of prostate cancer. To resolve this question, a larger number of cases and a longer follow-up period would be helpful, especially in view of the very long latency period and preclinical phase of prostate cancer.

A number of studies have evaluated the influence of dietary vitamin A and/or fruit and vegetable intake on prostate cancer risk, with conflicting results (Refs. 19–21 and 32–41; reviewed in Ref. 4). These discrepant findings may be related to methodological problems associated with dietary interview data and the problems in distinguishing vitamin A from carotenoids and other compounds abundant in plant sources. In addition, the contribution of dietary preformed vitamin A, found largely in dairy products, eggs, liver, and fortified cereals, is difficult to disentangle from other dietary components, notably fat and cholesterol.

Dietary intake of vitamin A is not highly correlated with serum levels, since vitamin A is under strict homeostatic control (22, 23, 42). Vitamin A is stored in the liver, its release mediated by binding to RBP. RBP levels are determined by a number of nutritional, hormonal, and disease-related factors including zinc levels (43, 44). In conditions of zinc deprivation the level of RBP decreases (44, 45). The normal prostate has an extremely high zinc concentration, while in prostate cancer the tissue levels appear to decrease by about two-thirds (46). A role has been postulated for disturbances in the balance of vitamin A, zinc, and RBP in the etiology of prostate cancer (9, 32). However, other processes may be involved. Vitamin A plays a role in maintenance of reproductive function and in differentiation of epithelium, including that of the prostate. In rodents, vitamin A deprivation leads to abnormalities of spermatogenesis, lowered testosterone levels, and squamous metaplasia of the prostate (47, 48). Retinol has been shown to exert a variety of cancer-inhibitory effects in animal model systems (49, 50) and to prevent or reverse some characteristics of the transformed state in cell culture (51). Further studies to evaluate nutritional, endocrine, metabolic, and other regulators of vitamin A homeostasis may help define the mechanisms of prostatic carcinogenesis.

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